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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,138	10/26/2000	Jens Fogh	FOGH1	5676

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	19

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/601,138	FOGH ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *Claims 1-19, 21-32 and 35-51* is/are pending in the application.

4a) Of the above claim(s) *38-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-32,35-37 and 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12, 16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The examiner is acknowledging the Amendment under Rule 1.115, filed on July 8, 2002 as paper No. 17. The amendments to the specification and claims have been entered. Claim 20 is cancelled. Claims 1, 3, 4, 5, 21, 23, and 40 are amended. New claims 47-51 are added. Claims 38-46 are withdrawn from consideration by examiner as directed to the non-elected invention; see 37 CFR 1.142(b). Claims 1,2, 3-19, 21-32, 35-37 and 47-51 in part related to acute intermittent porphyria (AIP) and the respective enzyme, porphobilinogen deaminase (PBGD), are the subject of this Office Action.

Detailed Office Action

1. Formal Matters

The copy of IDS, paper No.12, with initialed AF and AN positions is attached to this Office Action.

2. Election/Restriction

In their Remarks (paragraph 2.1.) Applicants write, "Examiner's position is that since restriction between the gene and the protein per se would have been proper, restriction between a method of using the gene and a method of using the protein is likewise proper. The ISA/EPO and IPEA/EPO viewed the matter differently, and we agree with them."

The Applicant is kindly reminded that the ISA/EPO opinions are not binding for the examiner of the 371application. It is reiterated herein that 37 CFR rule 1.475 (d) does not provide for multiple processes of use in the national stage application.

3. Objections

The amended claim 44 should be numbered 45 and depend on claim 44.

Claim 46 should depend on claim 44.

4. Rejections

4. 1. 35 U.S.C. 112, second paragraph

Claim 21, 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "small enzyme" in claim 21 is a relative term which renders the claim indefinite. The term "small enzyme" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unknown what the molecular weight of the enzyme has to be to be included or excluded from the scope of invention.

The terms "at least part " in claims 24 and 51, and "substantially all" in claim 24 are relative terms which render the claims indefinite. The term "at least part" or "substantially all" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unknown how much enzymatic activity should be exerted intracellularly to be included or excluded from the

scope of invention. For example if 99% of the activity is exerted intracellularly is it included in the scope of claim 22? Similarly, in case of claim 24, is, for example, 60% exerted in blood stream substantially all or only 99% and more is substantially all?

In their traversal of the last Office Action's rejection of claim 20 based on indefinitness of the phrase "at least part of the enzymatic activity ", Applicants state, "in any event relative phrases are not per se indefinite" (page 8, line 20). This argument is found not persuasive, because the relative term, unless defined by the specification is indefinite and the claim has to be rejected under 35 USC section 112, second paragraph.

Claims 36 and 37 are rejected as reciting the phrase "based on any of SEQ ID NO: 1 and SEQ ID NO:12". The phrase "based on SEQ ID NO: 1" is confusing. The sequence itself or its open reading frame encodes a protein.

Claim 25 is rejected because it does not further limit claim 24 from which it depends. The metabolic product of the action of the catalyst can only be either converted further via the remaining steps of heme biosyntethic pathway or excreted form an organism via urine and/or faeces. That is the very nature of physiology.

In addition, claims 2 and 47 are confusing because they recite particular diseaseses to be treated, but do not identify the relevant enzyme to be used for treatment.

Furthermore, clam 3 confusing because it recites particular enzymes used for the treatment, but does not identify the relevant disease to be treated.

Rejection withdrawal

Rejection of claims 1-32 and 35-37 under 35 U.S.C. 112, second paragraph, made in the previous Office Action, paper No. 13 as being indefinite for the use of the terms:

(1) enzymatically equivalent part thereof, and

(2) analog,

is withdrawn because the claims have been amended.

Rejection of claim 20 is moot because the claim has been canceled.

Rejection of claim 23 is withdrawn because the claim has been amended.

3.2. 35 U.S.C. 112, first paragraph

3.2.1. Lack of written description

Claim 1--19, 21-32, 35 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is generic since it is directed to a large genus of method of treatment or prophylaxis of disease caused by deficiency of enzyme belonging to the heme

biosynthetic pathway, wherein said methods use a genus of catalysts that are enzymes involved in the hem biosynthetic pathway, their mutants or enzymatically active fragments or analogs thereof. The claim does not identify any deficiency to be treated or a specific enzyme involved. The genus of enzymes and their active fragments and analogs to be used in the methods is a large variable genus, however Applicant provides only two representatives of the claimed genus of enzymes, the human PBGD encoded by SEQ ID NO:1 and 12. Other enzymes are mentioned by their functions, however Applicants do not teach which enzyme is encoded by which DNA sequence of the sequence listing provided in the application. Having at hands two representative species of the claimed genus is not sufficient for providing identifying characteristics of any species of the claimed genus, including fragments, mutants that retain desied biologic activity and synthetic enzymes. Even in case of PBGD, the elected species, the fragment having the catalytic activity is not discribed by the Applicants.

In addition, claim 2 and 47 describes the particular disease to be treated, but does not identify the relevant enzyme to be used for treatment.

Furthermore, clam 3 describes the particular enzymes used for the treatment, but does not identify the relevant disease to be treated.

Claims 21 and 22 remain rejected for reasons indicated in the previous Office Action, paper No.13. The reasons are reiterated herein.

The claims are directed to method for treatment or prophylaxis of a disease caused by deficiency an enzyme belonging to the heme biosynthesis pathway, the

method comprising administering an effective amount of a catalyst or an enzymaticaly equivalent part or analogue thereof wherein:

a) the catalyst is an artificial enzyme or any organic catalyst that can polymerize porphobilinogen to hydroxymethylbilane (claim 21),

b) the catalyst is formulated in such a manner that it exerts its activity intracellularly (claim 22).

Neither claim 21 nor the specification describe any small artificial enzyme or any organic catalyst that can polymerize porphobilinogen to hydroxymethylbilane.

Also, neither claim 22 nor the specification described the manner of formulation of the PDGD or any other catalyst so that it exerted at least part of its enzymatic activity intracellularly upon administration to the subject.

In their response Applicants argue, "However, enzymes are known to have multiple domains and, even within the enzymatic domain, it is not unusual to identiy enzymatically active fragments. P13, L20 teaches 'that the catalyst may be an 'enzymatically equivalent part' of an enzyme" (page 7 line 17).

Applicant argument is not found persuasive, because Applicants did not discribed any fragment of any enzyme that participate in any step of heme synthesis, wherein said fragment could be treated as "a small enzyme".

Claim 48, 49, 50 and 51 are rejected because neither the claims nor the specification disclose any enzymatically active fragment of PBGD or analogs thereof. The application quotes some papers disclosing variants of human PBGD, but these articles are not incorporated into the specification by reference. Applicants themselves cloned human erythro- and non-erythro-forms of PBGD DNA, however, the enzymatically active fragments of the molecules of these enzymes are not determined by Applicants.

In summary, because claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, the claims are rejected.

Rejections withdrawn

Rejection of claims 17 and 19-20 made in the previous office Action paper. No. 13 is withdrawn, because the Applicants' arguments have been found persuasive.

3.2.2. Scope of enablement

Claims 1-20, 22-31, 32, 35, and 47-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method for treatment or prophylaxis of acute intermittent porphyria (AIP) by administering to the subject an effective amount of porphobilinogen deaminase (PBGD) encoded by SEQ ID NO:1 or 12 does not reasonably provide enablement for the method to treat any disease caused

by deficiency of at least eight other enzymes belonging to the heme biosynthetic pathway, when the enzyme originate from any biologic or man-made source or is an enzymatically active fragment or analogue thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the treatment of human clinical conditions with huge number of all known and unknown enzymes of the heme biosynthetic pathway, their enzymatically active fragment, mutant and analogs enzymes from all existing organisms as well as engineered and synthetic. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses methods of treatment of any of human clinical conditions related to the impairment in any step of heme biosynthesis in human and non human subject, with an extremely large number of all known and unknown enzymes of the heme biosynthetic pathway from all appropriate

organisms, including more than 100 human allelic variants as well as enzymes that are recombinant, fragments and synthetic. While methods of gene cloning and expressing, as well as testing enzymatic activities are well known in the relevant art and skills of the artisans are highly developed, screening of an extremely large number of known enzymes of the heme biosynthetic pathway for its use in human clinical conditions, as well as screening genomic and cDNA libraries from relevant organism and man-made for the DNAs encoding any enzymes of the heme biosynthetic pathway that are unknown, expressing and isolating these enzymes and using them for treatment of subject in need is not within the realm of routine experimentation. In addition undue experimentation requires deterimination of enzymaticaly active domains of said proteins and their recombinant multiplication so that they could be used in therapy.

The working examples do not provide the amino acid sequences of suitable enzymes or other identifying characteristic thereof. The only teaching regarding the amino acid sequences are DNAs of SEQ ID NO:1 and 12 isolated by Applicants from human cells. However, Applicants do not provide any guidance regarding structure of their fragments having enzymatic activity. It is important to note that human PBGD was known to have more than 100 allelic variants at the time Applicants filed the application and not all variants were usefull for the treatment because they themselves my had impaired activity. In addition, none of the suitable synthetic enzyme is tought by Applicants. Absent these teachings one skilled in the art is forced to perform improperly extensive and undue experimentation.

In their response to rejection for lack of enablement for treatment with other enzymes Applicants argue that AIP can be also caused by deficiency of the enzymes other than PBGD and the casual relationship can be found (page 6, line 9). However, the disclosure is silent about such possibility. Rising this new matter would certainly require undue experimentation because the approach is completely not enabled. Thus, Applicants argument is found not persuasive.

3.3. 35 USC, section 103

Claims 1-19, 22-31, 32, 35 and 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raich et al. "Molecular cloning and complete primary sequence of human erythrocyte porphobilinogen deaminase " (*Nucleic Acid Research*, 1986, 14, 5955-5698) and further in view of many publications on enzyme replacement therapy, for example Beutler E. et al, "Enzyme replacement therapy for Gaucher Disease" (*Blood*, 1991, 78, 1183-1189).

The claims of the instant application are directed to the enzyme replacement therapy of acute intermittent porphyria a genetic disease in which the porphobilinogen deaminase is defective.

The PBGD gene has been cloned and sequenced for the first time by Raich et al. Raich et al teach that deficiency of PBGD is responsible for the disease AIP. However Raich et al do not teach enzyme replacement therapy with PBGD in AIP cases.

Beutler et al teach that the enzyme replacement therapy has been very succesful in treating patients suffering from another genetic defect manifested as Gaucher disease.

It would have been obvious to one having ordinary skill in the art at the time of the invention to express the gene taught by Raich et al, to obtain PBGD protein and administer it to the subject having the defective form of the enzyme, similarily as taught by Beutler et al in case of Gaucher disease.

The motivation would be, in the light of long felt need, to provide a treatment of AIP that is more efficient than the methods used thus far. The expectation of success is also provided by Beutler et al who teach that the enzyme replacement therapy results in marked regression of pathologic changes and general improvement in patients' health.

Addressing prior art issues on page 5 of the Remarks, Applicants write, "Reich is parroting the teachings of his reference (2), which is Meyer (1972). "Further Applicants note: "We believe that replacement therapy has been known since 1966.... The existence of a longfelt need for AIP therapy, coupled with the long term failure of others to apply the concept of replacement therapy to AIP once Reich taught the PBGD/AIP relationship, is objective evidence of nonobviousness."

Applicants arguments have been fully considerd but are found not persuasive for the following reasons.

1) As long as the reference is a prior art, and this is the case, "parroting" is irrelevant.

2) Beutler et al.'s article is a prior art, so it is irrelevant that this article is not the first one on the subject of enzyme replacement therapy.

3) The fact that prior art of record does not present the concept of replacement therapy to AIP is not a proof of nonobviousness of the concept. Applicants quotation of two additional prior art on enzyme replacement therapy only strengthens the fact that this therapy was obvious at the time of filling of the instant application.

In conclusion, in the current state of art, the enzyme replacement therapy may be non-obvious

only when the enzyme to be used is novel.

4. Conclusion

No claim is allowable, however the claims contain allowable subject matter. The following is examiner reason for indicating allowable subject matter. Applicants disclose novel DNA sequences of SEQ ID NO:1 and 12 that encode novel variants of human PBGD protein that can be used in the claimed method of treatment of acute intermittent porphyria. Because the enzymes are encoded by novel sequences application of the enzymes encoded by them to the treatment of AIP would be novel.

As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

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Art Unit 1652

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